IUBMB Enzyme Nomenclature

EC 1.3.1.2

Common name: dihydropyrimidine dehydrogenase (NADP)

Reaction: 5,6-dihydrouracil + NADP = uracil + $NADPH_2$

Other name(s): dihydrothymine dehydrogenase; dihydrouracil dehydrogenase (NADP); 4,5-dihydrothymine: oxidoreductase; DPD; DHPDH; dehydrogenase, dihydrouracil (nicotinamide adenine dinucleotide phosphate); dihydrouracil dehydrogenase (NADP); DHU dehydrogenase; hydropyrimidine dehydrogenase

Systematic name: 5,6-dihydrouracil:NADP 5-oxidoreductase

Comments: Also acts on dihydrothymine.

Links to other databases: BRENDA, EXPASY, KEGG, WIT, CAS registry number: 9029-01-0

References:

1. Fritzson, P. Properties and assay of dihydrouracil dehydrogenase of rat liver. *J. Biol. Chem.* 235 (1960) 719-725.

2. Shiotani, T. and Weber, G. Purification and properties of dihydrothymine dehydrogenase from rat liver. *J. Biol. Chem.* 256 (1981) 219-224. [Medline UI: 81093928]

[EC 1.3.1.2 created 1961, modified 1986]

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(54) Title: DIHYDROPYRIMIDINE DEHYDROGENASE COMPOSITIONS AND METHODS OF USE

(57) Abstract

Disclosed are methods and compositions for use in detecting and quantifying the enzyme dihydropyrimidine dehydrogenase (DPD) for use in, e.g., optimizing 5-fluorouracil doses given to cancer patients. Particularly described are antibodies, including monoclonal antibodies, to the human form of DPD; DNA sequences from bovine and human DPD; immunological and molecular biological means by which to detect DPD; and methods of designing effective cancer treatment strategies based upon information gained concerning DPD levels. Also disclosed is molecular characterization of a genetic lesion leading to DPD deficiency in humans and diagnostic methods for genetic screening of this mutation for patients undergoing FUra treatment.

2. DNA Sequence Analysis of DPD Gene in a DPD-Deficient Patient

Complete sequence analysis of the DPD deficient patient's cDNA also revealed an additional single nucleotide difference from that of control; A (control) to T (deficient) at position 2894. Translation of the cDNA demonstrated that this resulted in a nonconservative amino acid substitution (Asp to Val). Subsequent subcloning and sequence analysis of multiple PCR™ reactions flanking this region from a number of individuals having normal DPD activity demonstrated that this nucleotide substitution was common in the general population and may represent an allelic variant. In contrast, the adenosine deletion resulting in a frameshift was not found in any individuals having normal DPD activity but was identified exclusively in the DPD deficient patient's cDNA.

Since this deletion was initially identified in the cDNA of the DPD deficient patient (two out of the ten subclones), studies were undertaken with genomic DNA to confirm that this patient was heterozygous for this mutation. Primers were designed based on the cDNA sequence to amplify a 573 base pair DNA fragment from the exon containing the sequence of interest (FIG. 7A, FIG. 7B, FIG. 7C, and FIG. 7D). Sequence analysis of several clones (from multiple PCR™ reactions) from the deficient patient indicated the presence of two different alleles (one of these containing the deletion, the other identical to normal), present in approximately equal amounts. The identification of both the normal and mutant allele (adenosine deletion) in the genomic DNA confirm that this patient is heterozygous for the single base deletion.

In summary, the gene and the poly(A)+ RNA encoding the DPD protein in this patient contains an adenosine deletion that causes a frameshift resulting in truncation of translation at codon 335 generating a 36,500 dalton protein. Analysis of the patient's genomic DNA has demonstrated that this patient is heterozygous for this mutation. This represents the first molecular characterization of a DPD deficient patient, and provides an explanation for reduced DPD activity. This frameshift has also been identified in an additional unrelated DPD deficient patient who also exhibited severe FUra toxicity.